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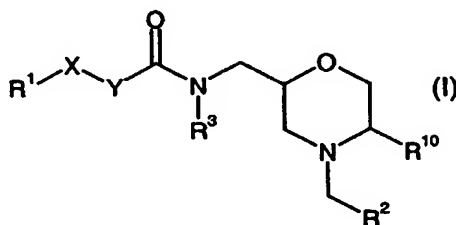
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Published:
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MORPHOLINE DERIVATIVES WITH A SUBSTITUTED ACETAMIDE GROUP IN THE 2-POSITION FOR USE AS CCR-3 ANTAGONISTS FOR THE TREATMENT OF INFLAMMATORY DISEASES



(57) Abstract: Certain compounds of formula (I); wherein R₁ represents substituted or unsubstituted aryl; X represents -O- or a bond; Y represents -(CR_{aa},R_{ab})_n; R_{aa} and R_{ab} are each independently hydrogen or C₁₋₆alkyl; n is an integer from 1 to 5; R² represents unsubstituted or substituted aryl or unsubstituted or substituted heteroaryl; R³ represents hydrogen or C₁₋₆alkyl; R¹⁰ represents hydrogen or C₁₋₆alkyl; and salts and solvates thereof are CCR3 antagonists and are therefore indicated to be useful in therapy of inflammatory conditions.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/03348

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/5377 A61K31/5375 A61P29/00 A61P11/06 C07D265/30
C07D413/12 C07D413/06 C07D209/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched, other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 02 26722 A (HARRISON LEE ANDREW ; JUDD DUNCAN BRUCE (GB); GLAXO GROUP LTD (GB);) 4 April 2002 (2002-04-04) examples claim 1	1-24
X	KATO S ET AL: "NOVEL BENZAMIDES AS SELECTIVE AND POTENT GASTRIC PROKINETIC AGENTS 1. SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF N-(2-MORPHOLINYL)ALKYLBENZAMIDES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 33, no. 5, May 1990 (1990-05), pages 1406-1413, XP001037844 ISSN: 0022-2623 example 9	19



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *Z* document member of the same patent family

Date of the actual completion of the international search

7 July 2003

Date of mailing of the international search report

18/07/2003

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/03348

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 00 31032 A (HOFFMANN LA ROCHE) 2 June 2000 (2000-06-02) page 2, line 25 - line 27; claim 1</p>	1-24

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 18,19 (part)

The compounds of claims 18 and 19 contain a substituent A, which is defined as a "protected amino group". However, this definition is only clear when the reaction conditions in which the amine remains protected, and those in which it is deprotected are specified. This is not the case in present claims 18 and 19. The broadest definition which is unambiguously clear has been used in the search, namely A = phthalimido (p. 28).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP 03/03348

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 23 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 18,19 (part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Publication No

PCT/EP 03/03348

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0226722	A	04-04-2002	AU 9014301 A	08-04-2002
			WO 0226722 A1	04-04-2002
			NO 20031442 A	26-05-2003
WO 0031032	A	02-06-2000	AU 1382500 A	13-06-2000
			BR 9915520 A	17-07-2001
			CA 2350903 A1	02-06-2000
			CN 1331677 T	16-01-2002
			CZ 20011760 A3	12-12-2001
			DE 19955794 A1	31-05-2000
			WO 0031032 A1	02-06-2000
			EP 1131288 A1	12-09-2001
			ES 2158814 A1	01-09-2001
			FR 2786185 A1	26-05-2000
			GB 2343893 A , B	24-05-2000
			HU 0104364 A2	29-04-2002
			IT T0991009 A1	21-05-2001
			JP 2002530374 T	17-09-2002
			NO 20012411 A	16-05-2001
			PL 348375 A1	20-05-2002
			TR 200101398 T2	21-09-2001
			US 6166015 A	26-12-2000